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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,610	12/13/2001	Kevin P. Baker	39780-2830P1C64	8144

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,610	BAKER ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-35,38-40 and 44-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-35,38-40 and 44-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/31/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, and/or Claims

The Amendments, submitted 31 August 2004 to 2 September 2004, have been entered into the record. Claims 33-35, 38, 39 and 44 are amended. Claims 36, 37 and 41-43 are cancelled. Claims 48-54 are added and read on the elected invention.

Claims 33-35, 38-40 and 44-54 are under examination in the Instant Application.

The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior Office action.

Withdrawn Objections And/or Rejections

URL's

The objection to the Specification because it contained browser-executable code, is *withdrawn.* Applicants amended the Specification to remove all URL's (2 September 2004).

35 USC § 112, first paragraph – Deposit Rules

The rejection of Claims 28-47 under 35 U.S.C. § 112, first paragraph, for not complying with the enablement requirement, is *withdrawn*. Applicants have submitted a copy of the ATCC deposit receipt (31 August 2004) and point out that the ATCC address is found in the Specification as filed (page 14, 2 September 2004).

35 U.S.C. § 112, first paragraph-, Written Description.

The rejection of Claims 28-47 under 35 U.S.C. § 112, first paragraph, Written Description, is *withdrawn*. Applicants canceled Claims 28-32, 38-40 and 44-47, thus rendering the rejection moot as to those claims. Applicants amended remaining claims to remove language pertaining to functional regions of SEQ ID NO: 352 that had not been identified (i.e., "extracellular domains") and removed references to nucleic acids having 80-99% sequence identity to the claimed PRO1755 nucleic acid (2 September 2004).

35 USC § 112, second paragraph

The rejection of Claims 28-47 under 35 U.S.C. 112, second paragraph, for being indefinite is *withdrawn*. Applicants cancelled 28-32, 38-40 and 44-47, thus rendering the rejection moot as to those claims. Applicants amended remaining claims to remove phrases pertaining to a peptide "extracellular domain" (2 September 2004) and added claim language precisely describing hybridization conditions supported by the Specification (2 September 2004).

Maintained Objections and/or Rejections

Continuity

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119. Applicants have argued that they are entitled to the benefit of Provisional Application 60/162,506. However, the Provisional patent applications listed, although disclosing the same experimental assays as the instant specification, do not

enable the instant invention and therefore do not impart Utility to the claims of the current application. Therefore, the filing date of 13 December 2001 is considered as the priority date.

35 U.S.C. § 101/112, first paragraph-, Lack of Utility, Enablement.

Claims 33-35, 38-40 and 44-54 are rejected under 35 U.S.C. 101, as lacking utility. The reasons for this rejection under *35 U.S.C. § 101* are set forth at pp. 3-7 of the previous Office Action (8 March 2004). Claims 33-35, 38-40 and 44-54 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Action (8 March 2004), one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue (Remarks/Arguments, 2 September 2004, pages 8-13) that the results presented in the instant Specification are enabling for the nucleic acids of SEQ ID NO: 351. They argue that the PRO1755 nucleic acid is a diagnostic marker for lung or colon tumors, and point to the results of the amplification assay which showed an approximately 2.5-fold amplification of the PRO1755 DNA in some lung or colon tumors (2 September 2004, page 11).

Applicant's arguments (2 September 2004) have been fully considered but are not found to be persuasive for the following reasons:

In the instant case, the specification provides data showing a very small increase in DNA copy number- about 2.5-fold- in 2 types of tumor. However, there is no evidence regarding whether or not PRO1755 mRNA or polypeptide levels are also increased in these cancers. Furthermore, as discussed in the previous Office Action (8 March 2004, page 7), what is often seen is a *lack* of correlation between DNA amplification and increased peptide levels (Pennica,

et al, 1998, Proc. Natl. Acad. Sci., 95: 14717-14722). As discussed by Haynes et al (1998, Electrophoresis, 19: 1862-1871), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to their results, the ratio varies from zero to 50-fold (page 1863). The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2: 405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Applicants argue (page 10, 2 September 2004) that "if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level," and then further discuss the Utility Guidelines (2001, 66 Fed. Reg. 1092). The Examiner has no authority to comment on the validity of the Patent Office Utility Guidelines and takes no issue with the general discussion concerning specific, substantial and credible utility of a claimed invention (pages 10 and 11, 2 September 2004). However, given the small increase in DNA copy number of PRO1755, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels or with a change in tissue function. Furthermore, since the PRO1755 peptide has no known role in the cell or in the organism, it

would not be useful to detect the PRO1755 nucleic acids. Further research needs to be done to determine whether the small increase in PRO1755 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,
>
> "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the Specification's assertions that the claimed PRO1755 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

Several Declarations under 37 CFR §1.132 were submitted with the current Response (31 August 2004).

The Declaration of Dr. Ashkenazi, filed under 37 CFR 1.132 (2 September 2004), is insufficient to overcome the rejection of claims 119-123, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action.

The Declaration of Dr. Polakis, filed under 37 CFR 1.132 (2 September 2004), is insufficient to overcome the rejection of claims 119-123, based upon, 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action.

The Declaration of Dr. Goddard, filed under 37 CFR 1.132 (2 September 2004), is insufficient to overcome the rejection of claims 119-123, based upon, 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action because:

In the Declaration filed under 37 CFR 1.132 (10 September 2004), staff scientist Ashkenazi claims that the purpose of the experiments that measured increases in gene copy number was to identify tumor cell markers useful for cancer treatment (page 1, Declaration, 16 June 2003) and to identify cancers for which there was an absence of gene product over-expression (page 2).

The Ashkenazi declaration filed under 37 CFR § 1.132 argues that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would be useful. However, as discussed above, there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial.

Dr. Polakis (declaration filed under 37 CFR § 1.132, 10 September 2004) states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in control tissues and that antibodies have been developed that

identify and could possibly be used to downregulate the PRO peptides. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. He characterizes the instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. Firstly, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO1755 in tumor samples as contrasted to normal tissue samples: Only gene amplification data were presented. As discussed above, and in the previous Office Action (page 5, 10 June 2004) this doubling of DNA levels in cancer tissue is probably due to a doubling of chromosome number, an event that is very common in cancerous tissues. In addition, it has not been shown that RNA or protein levels are increased in these two cancers. For these reasons, the Declaration is insufficient to overcome the rejection of claims 119-123 based upon 35 U.S.C. § 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Doctors Polakis and Ashkenazis' conclusions are provided in the declarations. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA Levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. See Hu et al. (2003, Journal of Proteome Research 2:405-412) as discussed above.

The declaration by Dr. Grimaldi has been fully considered but is not deemed persuasive. At paragraphs and 6, the declarant discusses the accuracy of the Taq DNA polymerase assay (Higuchi, et al, 1992, Biotechnology, 10: 413-417; Pennica et al, 1998, PNAS 95: 14717-14722; Pitti, et al, 1998, Nature, 396(6712): 699-703; Bieche, et al, 1998, Int. J. Cancer, 78: 661-666). and that the Taqman PCR technique is sensitive enough to detect at least a 2-fold increase in gene copy number (paragraph 7) and that this increase is significant and useful. This argument has been fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1755 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1755 nucleic acid was amplified in some lung or colon cancers, to a minor degree, of 2.5 fold increase. No mutation or translocation of PRO1755 has been associated with lung tumors or colon tumors. It is not known whether PRO1755 is expressed in normal lung or colon tissue, and what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1755 is amplified in a small number of samples, and invite the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates. It remains that, as evidenced by Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment.

Conclusion

No claims are allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire Later than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for

unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
16 November 2004

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER